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Experiments on the Combined Use of Crystal-Violet Vaccine and Anti-Hog-Cholera Serum in the Prevention of Hog Cholera

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INTRODUCTION

The principal disadvantage of crystal-violet vaccine for the prevention of hog cholera is the slow development of immunity in vaccinated pigs, at least 2 and sometimes 3 weeks being required for its full development. However, the immunity lasts for at least the life of market pigs and probably 12 months or longer. Treatment with anti-hog-cholera serum confers an immediate immunity, but it quickly wanes. Since serum confers an immediate but short immunity whereas crystal-violet vaccine confers a delayed but relatively lasting immunity, it would seem that a combination of the two treatments might retain the advantages and eliminate the disadvantages of the two methods of preventing hog cholera.

The possibility was investigated at the Ames, Iowa, field station of the Bureau by McBryde and Cole who, in 1936,[2] reported that when

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[1] The authors wish to thank C. N. Dale and L. O. Mott of the Pathological Division for their advice and suggestions during the investigations, and Clarence Cameron, of the Ames, Iowa, station, for assistance in compiling the data.

[2] McBryde, C. N., and Cole, C. G. crystal-violet vaccine for the prevention of hog cholera: progress report. Jour. Amer. Vet. Med. Assoc. (n. s. 42) 89 (6): 652–663. 1936.

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vaccinated pigs are given the usual protective dose of anti-hog-cholera serum, either simultaneously with vaccine or within 7 days after vaccination, the antigenic properties of the vaccine are inhibited by the serum.

Later investigations carried out at Ames have consistently confirmed the conclusion reached by McBryde and Cole. However, the use of serum and vaccine either simultaneously or first one and shortly afterward the other has been advocated and practiced since the vaccine first appeared on the market. In a recent paper, Doyle and Wright [3] reported that the results of an experiment carried out by them suggested that serum may be given 5 days before or after vaccine without inhibiting the antigenic action of the vaccine.

Seven experiments involving more than 247 pigs have been carried out at Ames in connection with studies of the combined use of serum and vaccine. Results of only two experiments have been published—one by McBryde and Cole [4] and the other by Cole and Henley.[5] Since the use of crystal-violet vaccine is increasing and there still seems to be confusion regarding its effectiveness when used with serum, the two previously published experiments are reported briefly in this circular, and the results obtained in other and later experiments are also presented.

EXPERIMENTAL PROCEDURE

The general plan of work in all experiments was to divide susceptible pigs into groups, to administer different treatments to the different groups, and later to inject the pigs in each group with hog-cholera virus. Treatments involved administration of serum alone, crystal-violet vaccine alone, serum and vaccine simultaneously, serum first and vaccine later, and vaccine first and serum later. In several instances pigs were treated first with vaccine and 7 days later with serum and virus and later exposed by a virus injection. Except for one group noted later, all injections of serum and vaccine were subcutaneous. Different doses of serum and vaccine were used in different groups. The interval between treatment and exposure to hog-cholera virus was 7 days in a few instances and about 90 days in the remainder. Pigs that remained normal for 14 days after injection were considered to be fully protected.

EARLY EXPERIMENTS

The first experiment was summarized by McBryde and Cole.[6] A slightly more detailed report of the treatments used and results obtained are given in table 1.

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[3] DOYLE, T. M., and WRIGHT, E. C. CRYSTAL-VIOLET SWINE FEVER VACCINE. Vet. Jour. 103 (12) : 406–417. 1947.

[4] See footnote 2.

[5] COLE C. G., and HENLEY, R. R. CRYSTAL-VIOLET HOG-CHOLERA VACCINE. U. S. Livestock Sanit. Assoc. Proc. Dec. 1946.

[6] See footnote 2.

TABLE 1.—*Methods of treatment and results obtained with 18 pigs in experiment 1, begun on Mar. 17, 1936*

Group	Pigs in group	Method of treatment	Results of exposure to 1 cc. hog-cholera virus 92 days after first treatment	Pigs adequately protected[1]
	Number			*Percent*
A	4	10 cc. vaccine first day; 35 cc. serum and 2 cc. virus 7 days later.	All remained normal	100
B	4	10 cc. vaccine first day; 35 cc. serum 7 days later.	3 had slight reaction; 1 was severely affected and was killed.	75
C	2	10 cc. vaccine first day	Both remained normal	100
D	2	35 cc. serum first day	Both were severely affected and were killed.	0
E	4	10 cc. vaccine and 35 cc. serum simultaneously, first day.	3 were severely affected and were killed; 1 died.	0
F	2	None	Both developed typical cholera and were killed for virus.	0

[1] Pigs that remained normal or had only slight reaction are reported as adequately protected.

Table 1 shows that the group treated with vaccine alone, as well as the group that received vaccine followed by serum and virus, remained well after exposure to hog cholera 92 days later, but that the four pigs treated simultaneously with vaccine and serum died or were killed because of being severely affected after exposure. The group treated first with vaccine and 7 days later with serum was found to be partly protected when exposed. The vaccine had probably produced partial immunity by the time the serum was administered. Since the group treated with vaccine alone remained well after exposure whereas the group that received vaccine and serum simultaneously developed cholera, the serum appeared to have interfered with the action of the vaccine.

Although only one experiment was reported by McBryde and Cole, two other experiments were carried out by them. The treatments used and the results obtained in the second and third experiments are given in tables 2 and 3, respectively.

TABLE 2.—*Methods of treatment and results obtained with 25 pigs in experiment 2, begun on July 17, 1936*

Group	Pigs in group	Method of treatment	Results of exposure to 1 cc. hog-cholera virus 92 days after first treatment	Pigs adequately protected [1]
	Number			*Percent*
A	4	10 cc. vaccine first day; 35 cc. serum 3 days later.	3 had severe reaction; 1 died.	0
B	4	10 cc. vaccine first day; 35 cc. serum and 2 cc. virus 3 days later.	All remained normal	100
C	4	10 cc. vaccine first day; 35 cc. serum 7 days later.	1 had slight reaction; 2 had severe reaction; 1 died.	25
D	4	10 cc. vaccine first day; 35 cc. serum and 2 cc. virus 7 days later.	All remained normal	100
E	2	10 cc. vaccine first day	Both remained normal	100
F	2	35 cc. serum first day	1 had severe reaction; 1 died.	0
G	3	10 cc. vaccine and 35 cc. serum simultaneously first day.	1 remained normal; 1 had slight reaction; 1 was killed moribund.	66
H	2	None	1 was severely affected and was killed; 1 died.	0

[1] Pigs that remained normal or had only slight reaction are reported as adequately protected.

TABLE 3.—*Methods of treatment and results obtained with 12 pigs in experiment 3, begun on Nov. 11, 1936*

Group	Pigs in group	Method of treatment	Results of exposure to 1 cc. hog-cholera virus 92 days after first treatment [1]	Pigs adequately protected [2]
	Number			*Percent*
A	2	40 cc. serum first day; 10 cc. vaccine 7 days later.	Both had severe reaction	0
B	2	40 cc. serum first day; 10 cc. vaccine 14 days later.	do	0
C	2	40 cc. serum first day; 10 cc. vaccine 21 days later.	1 had severe reaction; 1 died.	0
D	2	40 cc. serum first day; 10 cc. vaccine 28 days later.	Both had severe reaction	0
E	4	10 cc. vaccine first day; 40 cc. serum 14 days later.	All remained normal	100

[1] Group E exposed 106 days after first treatment, or 92 days after last treatment.
[2] Pigs that remained normal or had only slight reaction are reported as adequately protected.

In experiment 2, as in experiment 1, the groups treated with vaccine alone and with vaccine followed by serum and virus were the only ones in which all pigs remained normal when exposed to cholera 92 days after treatment. As in experiment 1 also, there appeared to be some interference by the serum when it was administered simultaneously with vaccine or 3 to 7 days later. Two of three pigs that received serum and vaccine simultaneously were adequately protected, whereas 7 of 8 pigs that received vaccine first and serum 3 to 7 days later developed acute cholera.

The pigs in all groups of experiment 3 in which serum was administered 1, 2, 3, or 4 weeks prior to vaccine treatment developed cholera after exposure. One died and the others recovered after severe reactions. Since only 1 pig died, it seems likely that a slight protection was afforded by the treatment. Group E, which was treated with the same vaccine 2 weeks prior to serum administration, was completely protected. In this experiment, pigs treated first with serum and 1 to 4 weeks thereafter with vaccine failed to develop a lasting immunity. Further, in this experiment pigs were treated for the first time with vaccine and 2 weeks later with serum and they developed a lasting immunity.

The results of these 3 experiments led to the previously mentioned published conclusion of McBryde and Cole[6] that serum interfered with the action of vaccine. However, the combined serum-vaccine treatment continued to be used by veterinarians and to be recommended by commercial producers of vaccine. Since the conclusion was based upon the results of only 3 experiments involving only 55 pigs, it was decided in 1946 to carry out a fourth experiment with combined serum and vaccine treatment. A description of this experiment and discussion of the results were published by Cole and Henley.[7] A table of results, however, was not published. For convenience, therefore, the treatments used and results obtained are summarized in table 4.

The results of the fourth experiment were in line with those of previous experiments. Thus, on exposure to hog cholera 92 days after treatment, no evidence of immunity was found in the groups treated with serum alone, with serum and vaccine simultaneously, or with serum first followed 1, 2, 3, or 4 weeks later with vaccine. Nor was there evidence of immunity at 92 days after treatment in the group treated with vaccine 1 week before serum was administered. Protection ranging from 80 to 100 percent was observed 92 days after treatment in the groups treated first with vaccine followed 2, 3, or 4 weeks later with serum. It is possible that in these groups immunity was developed from the use of vaccine before serum was administered. No practical purpose would be gained by treating first with vaccine and 2 or more weeks later with serum. If immunity had had time to develop from the use of vaccine, serum would not be needed; but if there had not been time for immunity to develop, it would in all likelihood be prevented if serum were given. One pig in the group receiving only vaccine had a severe reaction, but the symptoms—vomiting and loss of appetite without fever—were not typical of the reaction resulting from hog-cholera virus.

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[6] See footnote 2.
[7] See footnote 4.

TABLE 4.—*Methods of treatment and results obtained with 60 pigs in experiment 4, begun on July 31, 1946*

Group	Pigs in group	Method of treatment	Results of exposure to 2 cc. hog-cholera virus 92 days after first treatment	Pigs adequately protected [1]
	Number			*Percent*
A	5	35 cc. serum first day	All died	0
B	5	8 cc. vaccine first day	2 remained normal; 2 had slight reaction; 1 had severe reaction.	80
C	5	8 cc. vaccine and 35 cc. serum simultaneously first day.	All died	0
D	5	35 cc. serum first day; 8 cc. vaccine 7 days later.	2 had severe reaction; 3 died.	0
E	5	35 cc. serum first day; 8 cc. vaccine 14 days later.	do	0
F	5	35 cc. serum first day; 8 cc. vaccine 21 days later.	1 remained normal; 1 had slight reaction; 3 died.	40
G	5	35 cc. serum first day; 8 cc. vaccine 28 days later.	1 had severe reaction; 4 died	0
H	5	8 cc. vaccine first day; 35 cc. serum 7 days later.	3 had severe reaction; 2 died	0
I	5	8 cc. vaccine first day; 35 cc. serum 14 days later.	1 remained normal; 3 had slight reaction; 1 died.	80
J	5	8 cc. vaccine first day; 35 cc. serum 21 days later.	4 remained normal; 1 had slight reaction.	100
K	5	8 cc. vaccine first day; 35 cc. serum 28 days later.	All remained normal	100
L	5	None	1 had severe reaction; 4 died.	0

[1] Pigs that remained normal or had only slight reaction are reported as adequately protected.

The fourth experiment led to the conclusion announced at the 1946 meeting of the United States Livestock Sanitary Association [8] that it is useless to treat pigs with vaccine and serum simultaneously or with vaccine at any time within 4 weeks after serum treatment.

LATER EXPERIMENTS

About the time that the conclusion was announced, B. H. Edgington of the Ohio Agricultural Experiment Station reported at the 1946 Conference of Research Workers in Animal Diseases that many pigs treated with serum and vaccine and exposed 4½ or more weeks after treatment exhibited a high degree of protection. Full details of Dr. Edgington's experiments were later furnished by him to the Bureau. The serums, vaccines, and pigs used by Dr. Edgington were, of course, different from those used in the Bureau. Furthermore, in many cases the intervals between treatment and exposure also were different, the proportions of serum to vaccine used by him covered a wider range, and he obtained better immunity on late exposure when the proportion of serum to vaccine was small than when it was large.

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[8] See footnote 4.

In view of Dr. Edgington's findings, the investigation of the combined use of serum and vaccine was continued, particularly with reference to the effectiveness of different proportions of serum and vaccine. Further, it had been assumed in earlier work that the doses of serum used were sufficient to confer immediate immunity, and for that reason pigs had not been exposed shortly after treatment for the purpose of determining whether the serum administered had conferred immediate immunity. Accordingly, experiments 5, 6, and 7 were planned to determine the effects of different proportions of serum and vaccine and to test the immunity of the treated pigs shortly after as well as about 90 days after treatment.

In experiment 5, 56 pigs were divided into 9 groups and the different groups were treated as indicated in table 5. Half of each group were exposed to hog cholera by virus injection 7 days after treatment, for the purpose of testing the immunity attributable to serum, and the other half of each group were exposed by virus injection 91 days after treatment for the purpose of testing the immunity attributable to vaccine. Results of exposure are shown in table 5.

Among the pigs exposed 7 days after treatment, complete protection was found whenever the dose of serum was 15 cc. or more, regardless of whether it was administered alone, with 5 cc. of vaccine injected subcutaneously, or with 2½ cc. of vaccine injected intradermically. Since the immunity developed by the seventh day is attributable to serum, the action of the serum was not interfered with by the vaccine. Of the 16 pigs treated with serum and vaccine, all but 3 reacted when exposed 91 days after treatment—3 died, 1 was killed moribund, 7 had severe, and 2 had slight reactions. Since all the pigs treated with vaccine alone were adequately protected when exposed after 91 days, and since most of the pigs treated with serum and vaccine developed cholera, serum appeared to interfere with the action of vaccine, as was found in preceding experiments. Insofar as the proportion of serum to vaccine is concerned, the interference appeared less when the proportion was 1 to 1, as in group D, than when it was 3 or more to 1, as in groups E, F, and G. However, the differences were slight.

Experiment 6 was a repetition of that part of experiment 5 in which 5-cc. doses of serum, 5-cc. doses of vaccine, or both, were administered and in which exposures were made at 7 days. Results are shown in table 6.

TABLE 5.—*Methods of treatment and results obtained with 56 pigs in experiment 5, begun on June 10, 1947*

Group	Pigs in group	Method of treatment	Results of exposure to 2 cc. hog-cholera virus—					
			7 days after treatment			91 days after treatment		
			Pigs exposed	Reaction	Pigs adequately protected [1]	Pigs exposed	Reaction	Pigs adequately protected [1]
	Number		*Number*		*Percent*	*Number*		*Percent*
A	4	5 cc. serum	2	1 remained normal; 1 died.	50	2	Both died	0
B	4	15 cc. serum	2	Both remained normal	100	2	1 remained normal; 1 died	50
C	4	45 cc. serum	2	do	100	2	Both died	0
D	8	5 cc. serum and 5 cc. vaccine simultaneously.	4	1 had slight and 1 had severe reaction; 2 died.	25	4	1 remained normal; 1 had slight and 1 had severe reaction; 1 was killed moribund.	50
E	8	15 cc. serum and 5 cc. vaccine simultaneously.	4	All remained normal	100	4	1 remained normal; 3 had severe reaction.	25
F	8	45 cc. serum and 5 cc. vaccine simultaneously.	4	do	100	4	1 remained normal; 1 had severe reaction; 2 died.	25
G [2]	8	15 cc. serum and 2½ cc. vaccine simultaneously.	4	do	100	4	1 had slight and 2 had severe reaction; 1 died.	25
H	8	5 cc. vaccine	4	1 had slight and 3 had severe reaction.	25	4	3 remained normal and 1 had slight reaction.	100
I	4	None	2	Both died	0	2	Both died	0

[1] Pigs that remained normal or had only slight reaction are reported as adequately protected

[2] The pigs in this group were injected intradermically with vaccine. In all other groups and in all other experiments all injections were by the subcutaneous route.

TABLE 6.—*Methods of treatment and results obtained with 24 pigs in experiment 6, begun on July 17, 1947*

Group	Pigs in group	Method of treatment	Results of exposure to 2 cc. hog-cholera virus 7 days after first treatment	Pigs adequately protected[1]
	Number			*Percent*
A	4	5 cc. serum and 2 cc. virus simultaneously.[2]	------------------------	0
B	4	5 cc. serum	1 had severe reaction; 3 died	0
C	4	5 cc. vaccine	1 remained normal; 1 had slight reaction; 1 had severe reaction; 1 died.	50
D	8	5 cc. vaccine and 5 cc. serum simultaneously.	I had slight reaction; 7 died	12. 5
E	4	None	All developed typical cholera and were killed for virus.	0

[1] Pigs that remained normal or had only slight reaction are reported as adequately protected.

[2] 2 had severe reaction; 2 died.

Group C receiving 5 cc. of vaccine alone was 50 percent adequately protected, whereas Group D receiving 5 cc. of vaccine and 5 cc. of serum was only 12.5 percent adequately protected. This difference would indicate that serum, even in a nonprotective dose, interfered with the action of vaccine even when exposure was made as early as 7 days. Certainly the production of immediate immunity was not obtained by combining a small amount of serum with a standard dose of vaccine.

Experiment 7 consisted of a series of tests in which the dose of serum was 10 cc. for all pigs and the dose of vaccine ranged from 5 to 30 cc. In a preliminary test of the serum, four pigs were treated with 10-cc. doses followed 1 week later by 2 cc. of virus. Three remained normal and one was sick for 5 days, indicating that the 10-cc. dose was about a minimum protective dose.

In the final test, 52 pigs were divided into 7 groups. The size of each group and the treatment received are shown in table 7. One-half of the pigs of each group were exposed 7 days after treatment; the other half, 92 days after treatment. To determine whether 5 cc. of serum was sufficient to afford immediate protection against 2 cc. of virus, four pigs were treated simultaneously with those doses. Cholera developed before the seventh day. Two had severe reactions and two died. Results of all exposures are given in table 7.

TABLE 7.—*Methods of treatment and results obtained with 52 pigs in experiment 7, begun on Dec. 1, 1947*

Group	Pigs in group	Method of treatment	Results of exposure to 1 cc. hog-cholera virus—					
			7 days after treatment			92 days after treatment		
			Pigs exposed	Reaction	Pigs adequately protected [1]	Pigs exposed	Reaction	Pigs adequately protected [1]
	Number		*Number*		*Percent*	*Number*		*Percent*
A	8	10 cc. serum	4	All remained normal	100	4	1 had slight and 1 had severe reaction; 2 died.	25
B	8	10 cc. vaccine	4	2 remained normal; 2 had slight reaction.	100	4	All remained normal	100
C	8	10 cc. serum and 5 cc. vaccine simultaneously.	4	3 remained normal; 1 had slight reaction.	100	4	2 remained normal; 1 had severe reaction; 1 died.	50
D	8	10 cc. serum and 10 cc. vaccine simultaneously.	4	do	100	4	do	50
E	8	10 cc. serum and 20 cc. vaccine simultaneously.	4	do	100	4	2 remained normal; 2 had slight reaction.	100
F	8	10 cc. serum and 30 cc. vaccine simultaneously.	4	1 remained normal; 3 had slight reaction.	100	4	do	100
G	4	None	2	Both died	0	2	1 had severe reaction; 1 died	0

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[1] Pigs that remained normal or had only slight reaction are reportd as adequately protected.

Of the pigs exposed 7 days after treatment, the group receiving serum alone was the only one in which all pigs remained normal. The group that received the largest dose of vaccine along with 10 cc. of serum had the largest number of reactions. Although the reactions were slight they might suggest that vaccine interfered with the action of the serum. However, of the 16 pigs that received serum and vaccine, only 6, or 37.5 percent, had slight reactions. This is only slightly above the 25 percent that reacted in the preliminary test of the serum. Since none of the pigs died or had severe reactions, 100-percent adequate protection was attained in all pigs that received serum and vaccine and were exposed 7 days later. It may therefore be concluded that in these tests doses of vaccine up to 30 cc. did not interfere with the action of serum.

The group that received 10 cc. of vaccine alone and that was exposed 7 days later was 100-percent adequately protected since 2 pigs remained normal and 2 had slight reactions. The degree of protection indicated was higher than has been previously observed in vaccine-treated pigs 1 week after treatment. Since the vaccine alone conferred a high degree of protection by the seventh day, some of the immunity noted at this time in groups treated with serum and vaccine was due in part to the vaccine.

Of the pigs exposed 92 days after treatment, the group treated with vaccine alone was the only one in which all pigs remained normal. Slight to severe reactions or death occurred in pigs in the serum-vaccine-treated groups. Although the dose of serum was considered to be a minimum protective dose, it apparently interfered with the action of the vaccine. The interference ranged from a trace when 20- or 30-cc. doses of vaccine were used to as much as 50 percent when the dose was 5 or 10 cc. Groups E and F which, for all practical purposes, were found to be immune are the only serum-vaccine-treated groups that have exhibited a high degree of immunity when exposed about 90 days after treatment.

The proportion of serum to vaccine used in those groups (1 to 2 and 1 to 3) was smaller than had been previously used. In most instances the proportion of serum to vaccine was 3 or more to 1, and in all such instances the serum-vaccine-treated groups were found to lack immunity when exposed about 90 days after treatment. The results, therefore, like Dr. Edgington's, indicate that with pigs treated with serum and vaccine a better late immunity is obtained when the proportion of serum to vaccine is small than when it is large.

DISCUSSION

No justification for the combined use of crystal-violet vaccine and anti-hog-cholera serum was found in the work reported in this circular. On the contrary, when adequate doses of serum were given along with standard doses of vaccines, the combined treatment was found to be harmful rather than beneficial. When unusually large doses (20 to 30 cc.) of vaccine were given along with a relatively small dose (10 cc.) of serum, the treated pigs exhibited adequate immunity when exposed after 92 days. No real advantages would be gained by using such doses. The procedure would be costly and since serums and vaccines vary from lot to lot in potency the correct doses to be used on different lots of pigs would have to be ascertained for such treatment.

The above remarks apply not only to simultaneous treatment with serum and vaccine but also to the administration of vaccine followed by serum or to the administration of serum followed by vaccine. As previously pointed out, if vaccine is given first and immunity has time to develop before serum is given, serum would not be needed. If immunity from the use of vaccine has not had time to develop, serum, if given in an adequate dose, would interfere with its development. The results also indicated that if serum is given first, it may interfere for at least 28 days with the action of vaccine. No advantage would be gained by giving serum first, waiting for its effects to disappear, and then giving vaccine. In such cases a lag would occur in the development of immunity just as a lag occurs when vaccine alone is administered.

Briefly, the lasting immunity that normally would be expected to develop when an adequate dose of vaccine was given failed to develop when a protective dose of serum was given along with the vaccine, indicating that serum interfered with vaccine. However, the immediate immunity that would be expected to develop when an adequate dose of serum was given always developed when vaccine, in any of the doses used, was given along with the serum, indicating that vaccine did not interfere with the action of serum.

SUMMARY AND CONCLUSIONS

Seven experiments were carried out at the Ames, Iowa, field station of the Bureau for the purpose of determining the effectiveness, in the prevention of hog cholera, of treatment with crystal-violet vaccine and anti-hog-cholera serum combined. In the experiments, 247 pigs were used. The principal methods of treatment were simultaneous use of serum and vaccine, use of serum first and then vaccine, vaccine first and then serum, serum alone, and vaccine alone. Doses of vaccine used ranged from 2½ to 30 cc. and the doses of serum from 5 to 45 cc. All the treated pigs were exposed to hog-cholera virus. In most of the experiments, all the pigs were exposed at one time—about 90 days after treatment. In a few experiments, half of the pigs that received a particular treatment were exposed 7 days after treatment; the other half, about 90 days after treatment. In one experiment, all pigs were exposed 7 days after treatment.

No evidence was found that vaccine interfered with the action of serum; that is, pigs treated with an adequate dose of serum and vaccine were found to be as well protected when exposed on the seventh day as were pigs that had been treated with similar doses of serum alone.

The results consistently indicated that serum interfered with the action of vaccine. The interference varied from very slight when small (10 cc.) doses of serum and large (20 to 30 cc.) doses of vaccine were used to 100 percent when normally adequate or standard (5 cc.) doses of vaccine were used along with standard (15 to 35 cc.) doses of serum.

The use of small doses of serum along with large doses of vaccine would not be recommended in general practice not only because of the cost involved, but also because there is no assurance that a particular proportion of serum and vaccine would be generally effective. No justification was therefore found for the combined use of serum and vaccine.

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